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09/712,768	11/14/2000	Akira Asakura	20511/111693	9077

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT PAPER NUMBER

1652

13

DATE MAILED: 02/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/712,768

Applicant(s)

ASAKURA ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-80 is/are pending in the application.
- 4a) Of the above claim(s) 1-21 and 51-56 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 22 and 23 is/are allowed.
- 6) ☒ Claim(s) 24-50 and 57-80 is/are rejected.
- 7) ☒ Claim(s) 50 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

The amendment filed November 13, 2002 amending the specification to replace the Sequence listing with a substitute Sequence Listing, to insert reference to the sequences identifiers, amending claims 24-32, 37, 40, 41, 44-46 and adding claims 57-80 has been entered.

The statement regarding the biological deposit is provided on page 28 of Remarks.

Claims 1-80 are pending. Claims 1-21 and 51-56 are withdrawn, claims 23-49 and 57-80 are under consideration.

Specification

The disclosure is objected to because of the following informalities: on page 15, "42EC" and "37EC" are typed where it appears "42°C" and "37°C" were intended.

Appropriate correction is required.

Claim Objections

Claim 50 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 50 recites a

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homolog of *Gluconobacter oxydans* DSM 4025, wherein said homolog is not included in the scope of claim 49 from which claim 50 depends.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-50, 58, 59 and 64-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a DNA fragment encoding SEQ ID NO:4, 6 or 8 wherein it encodes at least part of core subunit II or core subunit III of "a cytochrome c oxidase complex and that conveys cytochrome c oxidase activity when present", an expression vector and a recombinant microorganism comprising thereof. SEQ ID NO:4, 6 or 8 are 44, 38 and 29 amino acids in length and are encoded by SEQ ID NO: 3, 5 or 7, respectively. SEQ ID NO:4 is a fragment of cytochrome C II subunit (COII) and SEQ ID NOs: 6 and 8 are fragments of cytochrome C III subunit (COIII) from *Gluconobacter oxydans* DSM 4025. The specification teaches that COII has molecular mass about 36

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kD (page 3). From these and cloning data, it is apparent that the above sequences represent small fragments of the corresponding full-length sequences (e.g., pages 28-29; Figure 7).

Thus, the claims are drawn to or depend from a genus of polynucleotides comprising a polynucleotide encoding SEQ ID NO:4, 6 or 8 or homologous sequences that conveys cytochrome *c* oxidase activity when present.

The recited structural feature of the genus (i.e., encodes a fragment of 44, 38 or 29 amino acids) does not constitute a substantial portion of the genus as the remainder of the structure of a subunit that conveys cytochrome *c* oxidase activity when present with two other core subunits of cytochrome *c* oxidase from *Gluconobacter oxydans* DSM 4025 or to any other cytochrome *c* oxidase is completely undefined.

Fragments consisting of 44, 38 or 29 amino acids, respectively, are highly unlikely to convey a cytochrome *c* oxidase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected. This is different from a DNA encoding SEQ ID NO:2 that is a full length sequence of COI and as such conveys cytochrome *c* oxidase activity when present with two other core subunits of cytochrome *c* oxidase from *Gluconobacter oxydans* DSM 4025 .

The specification discloses only a single species of the claimed genus, COII subunit from *Gluconobacter oxydans* DSM 4025 comprising SEQ ID NO: 4 and COIII subunit from *Gluconobacter oxydans* DSM 4025 comprising SEQ ID NOs: 6 and 8, and

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fails to provide any structure: function correlation present in all members of the claimed genus. As such, the disclosure of DNAs encoding SEQ ID NOs: 3, 5 and 7 is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus that comprises the above sequences and encodes a core subunit that conveys cytochrome c oxidase activity when present with two other core subunits of cytochrome c oxidase from *Gluconobacter oxydans* DSM 4025 or to any other cytochrome c oxidase. One skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 24-50 and 57-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA fragment encoding SEQ ID NO: 2, 4, 6 or 8, does not reasonably provide enablement for a DNA comprising DNA fragment encoding SEQ ID NO: 4, 6 or 8 or a sequence that is 85% identical thereto or a DNA that hybridizes thereto under highly stringent conditions and that conveys cytochrome c oxidase activity when present with two other core subunits of cytochrome c oxidase from *Gluconobacter oxydans* DSM 4025 or to any other cytochrome c oxidase. It does not reasonably provide enablement for a DNA fragment encoding a sequence that is 85% identical to SEQ ID NO: 2 or a DNA that hybridizes thereto under highly stringent conditions and encodes a core subunit that conveys cytochrome c

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oxidase activity when present to any cytochrome c oxidase other than from *Gluconobacter oxydans* DSM 4025. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNAs encoding polypeptides comprising SEQ ID NO: 4, 6 or 8 or a sequence that is 85% identical thereto or DNAs that hybridize thereto under highly stringent conditions that convey cytochrome c oxidase activity when present to any cytochrome c oxidase including when present with two additional core subunits from *Gluconobacter oxydans* DSM 4025.

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With regard to DNAs encoding core subunits comprising SEQ ID NO: 4, 6 or 8 or a sequence that is 85% identical thereto or DNAs that hybridize thereto under highly stringent conditions and retaining *Gluconobacter oxydans* DSM 4025 COII and/or COIII activity, the specification does not support the broad scope of the claims because the specification does not establish: (a) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired enzymatic activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

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Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins or genes where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

With regard to DNAs comprising DNAs encoding polypeptides comprising SEQ ID NO: 2, 4, 6 or 8 or a sequence that is 85% identical thereto or DNAs that hybridize thereto under highly stringent conditions that convey cytochrome c oxidase activity when present to any cytochrome c oxidase other than when present with two additional core subunits from *Gluconobacter oxydans* DSM 4025, the specification does not provide a guidance as to other subunits of cytochrome c oxidase that must be present. The art teaches that cytochrome c oxidases are enzymatic complexes comprising different number of subunits including different number of "core" subunits (the specification, pages 1-2). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which structure would impart the desired activity requires a detailed knowledge of the ways in which the proteins' structure relates to its function and vice versa. The disclosure lacks any information regarding the correlation between the requisite function and structure(s) of other subunit(s) that must be present in the complex.

Thus, one of ordinary skill in the art would require guidance, in order to make a DNA fragment encoding a polypeptide retaining *Gluconobacter oxydans* DSM 4025

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COII or COIII function or conveying the requisite function to any cytochrome c oxidase and having any structure comprising SEQ ID NO: 4, 6 or 8 or homologous sequences, in a manner reasonably correlated with the scope of the claims.

Furthermore, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a DNA fragment that comprises a DNA encoding a sequence that is 85% identical to SEQ ID NO: 2 or hybridizes thereto under highly stringent conditions and that conveys cytochrome c oxidase activity when present to any cytochrome c oxidase other than when present with COII and COIII from *Gluconobacter oxydans* DSM 4025. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-50, 57-62, 64-66, 68-70 and 72-80 and are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31, with dependent claims 33-39, is confusing as it is unclear whether a DNA that encodes several subunits or one subunit is implied. Amending the claim to

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replace "and" with "or" on line 2 in "subunits I, II and III" and replacing "or" with "and" on line 6 is suggested.

Claims 32 and 40-50 are confusing as it is unclear whether a DNA that encodes several subunits or one subunit is implied. Amending the claims to replace "and" with "or" on line 2 in "subunits I, II and III". Further, it is unclear which "combinations thereof" are encompassed by the claims except for two additional subunits present in the complex.

Claims 57-59 contain brackets that are not allowed in the claims. Amending the claims to delete brackets and insert "comprising" after "high stringency conditions" is suggested. The recitation of "gentle rocking" is not necessary since this is well known because the solution contains radioactivity.

With regard to claim 60, it is unclear whether one recombinant DNA and two non-recombinant DNAs are encompassed by the term "complex".

With regard to claims 61, 65, 69, 73, 76 and 79, core subunits are not "properties". The complex comprises them.

In claims 62, 66, 70, 74, 77 and 80, it is unclear which enzymes other than "cytochrome c oxidase" are encompassed.

With regard to claims 64, 68, 72, 75 and 78, a DNA is either recombinant or isolated. If one subunit is recombinant the entire complex is not isolated.

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Allowable Subject Matter

Claims 22 and 23 are allowed.

Response to Arguments

Applicant's arguments filed November 13, 2002 have been fully considered but they are not persuasive.

With regard to the written description, Applicants argue that "in view of the ***structural recitation of the specific polynucleotide and polypeptide sequences*** in the claims, the ***specific function*** for the encoded polypeptides recited by the claims, and the cytochrome c oxidase activity assay disclosed in the specification, the claims as amended are in compliance with the written description requirement of § 112, first paragraph" (Remarks, page 24). This is not agreed with because as discussed in the rejection above, the recited structure is not responsible for the requisite function and, therefore, the correlation between the structure and function common to all members of the claimed genus is lacking. Moreover, in view of the diversity of cytochrome c oxidase complexes, the claimed function cannot be construed as specific. Further, while the cytochrome c oxidase activity assay may be disclosed in the specification, this does not add to the description of the claimed DNAs.

With regard to the enablement, applicants argue that the amended claims are enabled because they recite the specific function (pages 24-27). This is not agreed with

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because the function as claimed is not specific. As taught by Applicants and the art and discussed in the rejection above, different cytochrome c oxidase complexes comprise different subunits. Absent the knowledge of other subunits necessary for the function, it is impossible to make and/or use the claimed subunit. For example, SEQ ID NO:2 exhibits the requisite activity in the presence of both COII and COIII from *Gluconobacter oxydans* DSM 4025. It is unknown and unpredictable which are other polypeptides that being combined with SEQ ID NO:2 would exhibit the cytochrome c oxidase activity.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

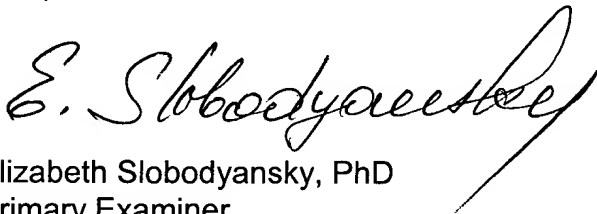
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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.



Elizabeth Slobodyansky, PhD
Primary Examiner

February 5, 2003